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# Longitudinal Associations among Renal Urea Clearance–Corrected Normalized Protein Catabolic Rate, Serum Albumin, and Mortality in Patients on Hemodialysis

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## Abstract

**Background and objectives** There are inconsistent reports on the association of dietary protein intake with serum albumin and outcomes among patients on hemodialysis. Using a new normalized protein catabolic rate (nPCR) variable accounting for residual renal urea clearance, we hypothesized that higher baseline nPCR and rise in nPCR would be associated with higher serum albumin and better survival among incident hemodialysis patients.

**Design, setting, participants, & measurements** Among 36,757 incident hemodialysis patients in a large United States dialysis organization, we examined baseline and change in renal urea clearance–corrected nPCR as a protein intake surrogate and modeled their associations with serum albumin and mortality over 5 years (1/2007–12/2011).

**Results** Median nPCRs with and without accounting for renal urea clearance at baseline were 0.94 and 0.78 g/kg per day, respectively (median within-patient difference, 0.14 [interquartile range, 0.07–0.23] g/kg per day). During a median follow-up period of 1.4 years, 8481 deaths were observed. Baseline renal urea clearance–corrected nPCR was associated with higher serum albumin and lower mortality in the fully adjusted model ( $P_{\text{trend}} < 0.001$ ). Among 13,895 patients with available data, greater rise in renal urea clearance–corrected nPCR during the first 6 months was also associated with attaining high serum albumin ( $\geq 3.8$  g/dl) and lower mortality ( $P_{\text{trend}} < 0.001$ ); compared with the reference group (a change of 0.1–0.2 g/kg per day), odds and hazard ratios were 0.53 (95% confidence interval, 0.44 to 0.63) and 1.32 (95% confidence interval, 1.14 to 1.54), respectively, among patients with a change of  $< -0.2$  g/kg per day and 1.62 (95% confidence interval, 1.35 to 1.96) and 0.76 (95% confidence interval, 0.64 to 0.90), respectively, among those with a change of  $\geq 0.5$  g/kg per day. Within a given category of nPCR without accounting for renal urea clearance, higher levels of renal urea clearance–corrected nPCR consistently showed lower mortality risk.

**Conclusions** Among incident hemodialysis patients, higher dietary protein intake represented by nPCR and its changes over time appear to be associated with increased serum albumin levels and greater survival. nPCR may be underestimated when not accounting for renal urea clearance. Compared with the conventional nPCR, renal urea clearance–corrected nPCR may be a better marker of mortality.

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## Introduction

Protein-energy wasting (PEW), manifested by inadequate dietary protein intake or low serum albumin, is a common condition and a predictor of mortality in patients on dialysis (1–4). PEW is characterized by simultaneous loss of body protein and energy stores among patients with advanced CKD (5–7). Among patients on dialysis, the protein requirement is higher than in healthy adults because of the removal of amino acid by the dialysis treatment and the protein catabolic or antianabolic state caused by the uremia, inflammation, oxidative stress, and exposure to bio-incompatible dialysis materials (8). The National Kidney Foundation Kidney Disease Outcomes Quality

Initiative (KDOQI) clinical practice guidelines recommend a dietary protein intake of 1.2 g protein per 1 kg of ideal body wt per day for patients on maintenance hemodialysis (9). However, the role of dietary protein intake on serum albumin levels remains controversial on the basis of current published data mostly from cross-sectional studies (10,11).

The urea kinetic–based protein catabolic rate, which is usually normalized for body weight (normalized protein catabolic rate [nPCR]), is often interpreted as a measure of dietary protein intake. During steady-state conditions, protein intake is equal to or slightly greater than nPCR (9). Although serum albumin is a strong predictor of mortality among incident and

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prevalent hemodialysis patients (2,12,13), the mortality predictability of nPCR in patients on hemodialysis remains controversial. A previous study of patients on hemodialysis showed that there was no association between mortality and either baseline or 6-month follow-up measurements of nPCR (14), whereas other studies have shown an increased risk of death among patients with low levels or decreasing trend in nPCR (15–18).

These inconsistent results may be partly due to the fact that previous studies calculated nPCR without accounting for the contribution of residual renal urea clearance ( $rCL_{urea}$ ) (19,20). In addition, most studies evaluated the association between nPCR and serum albumin in a cross-sectional manner. We, therefore, hypothesized that nPCR accounting for  $rCL_{urea}$  (*i.e.*,  $rCL_{urea}$ -corrected nPCR) provides better mortality risk stratification among incident hemodialysis patients while retaining its association with better survival and that a rise in nPCR, not baseline nPCR, is associated with attaining higher serum albumin.

## Materials and Methods

### Patients

We retrospectively analyzed clinical data from all incident in-center hemodialysis patients ages  $\geq 18$  years old treated in facilities operated by a large United States dialysis organization from January 1, 2007 to December 31, 2011 (21). Patient follow-up was divided into 20 consecutive patient-quarters representing 91-day intervals from the start of dialysis. Among 208,820 incident dialysis patients, we identified 133,134 patients who were treated only with conventional hemodialysis. We excluded patients with missing data on serum albumin, single-pool Kt/V (spKt/V), and  $rCL_{urea}$  at baseline and those with multiple measurements of BUN on the same day, resulting in a cohort of 36,757 patients for evaluation of the association between baseline nPCR and mortality (Supplemental Figure 1). Differences in baseline characteristics among included versus excluded patients are shown in Supplemental Table 1. We further restricted to 13,895 patients with available data on serum albumin, spKt/V, and  $rCL_{urea}$  at the third patient-quarter to evaluate the association of change in nPCR during the first 6 months of dialysis (*i.e.*, from the first quarter to the third quarter) with attained serum albumin  $\geq 3.8$  g/dl and mortality risk. The study was approved by the Institutional Review Committees of the University of California, Irvine and Los Angeles Biomedical Research Institute at Harbor–University of California, Los Angeles, with the exemption of obtaining written consent given the large sample size, anonymity of the patients studied, and noninvasive nature of the research.

### Demographic, Clinical, and Laboratory Measures

Information on demographics, cause of ESRD, access type, presence of comorbidities, and death was obtained from the large dialysis organization's database. Most blood samples were collected before dialysis. Dialysis dose was estimated by spKt/V using the urea kinetic model. Serum albumin was assayed using the bromocresol green method throughout the study period. The average serum urea concentrations during the urine collections were assumed to be 90% of the predialysis concentrations according to the approach by Daugirdas (22), and  $rCL_{urea}$  was calculated as

described with adjustment for body surface area (23,24) as presented in Supplemental Material. As an indicator of daily protein intake, nPCR was calculated accounting for  $rCL_{urea}$  (*i.e.*,  $rCL_{urea}$ -corrected nPCR) and expressed as  $nPCR_{dial+renal}$ . In contrast, nPCR calculated without accounting for  $rCL_{urea}$  (*i.e.*, non- $rCL_{urea}$ -corrected nPCR), as commonly used in current clinical practice, is expressed as  $nPCR_{dial}$ . To account for varying frequencies of dialysis treatments per week (two versus three times), the correction component for the predialysis BUN ( $C_0$ ) for  $nPCR_{dial+renal}$  and  $nPCR_{dial}$  equations is used as shown in Supplemental Material. To minimize measurement variability, all repeated measures for each patient during any given patient-quarter were averaged. The averaged values during the first patient-quarter were used as baseline data.

### Statistical Analyses

To examine differences between  $nPCR_{dial}$  and  $nPCR_{dial+renal}$  levels, we used the Bland–Altman plot and summarized the differences by  $rCL_{urea}$  strata ( $<1.5$ ,  $1.5$  to  $<3.0$ ,  $3.0$  to  $<4.5$ , and  $\geq 4.5$  ml/min per  $1.73$  m<sup>2</sup>). Baseline characteristics between the high and low baseline  $nPCR_{dial+renal}$  groups ( $<1.2$  and  $\geq 1.2$  ml/min per  $1.73$  m<sup>2</sup>, respectively) were summarized as proportions, means ( $\pm$ SD), or medians (interquartile ranges [IQRs]). Given the relatively large sample size of this study, baseline characteristics were compared by standardized differences, of which 0.2, 0.5, and 0.8 were considered small, medium, and large differences, respectively, and  $\geq 0.1$  was defined as a meaningful imbalance (25). Ten categories of baseline  $nPCR_{dial+renal}$  were created:  $<0.6$  and  $\geq 1.4$  g/kg per day and eight incremental categories of 0.1 g/kg per day in between. Likewise, change in  $nPCR_{dial+renal}$  from the first quarter to the third quarter of dialysis was calculated, and nine categories were created as follows:  $<-0.2$  and  $\geq 0.5$  g/kg per day and seven incremental categories of 0.1 g/kg per day in between.

Logistic regression models were used to estimate associations between baseline  $nPCR_{dial+renal}$  and having baseline serum albumin  $\geq 3.8$  g/dl and between change in  $nPCR_{dial+renal}$  and attained serum albumin  $\geq 3.8$  g/dl at the third patient-quarter. The Cox proportional hazards model was used to estimate the associations between the exposure categories and all-cause mortality. The hazard proportionality was confirmed by the Schoenfeld residuals plot. Both baseline  $nPCR_{dial+renal}$  and change in  $nPCR_{dial+renal}$  were also modeled as continuous variables, and their relationship with outcomes (mortality or attained serum albumin level  $\geq 3.8$  g/dl at the third patient-quarter) was estimated using restricted cubic spline functions with four knots at the fifth, 35th, 65th, and 95th percentiles of each index and referent at the median of  $nPCR_{dial+renal}$ . For each analysis, associations were adjusted by using three levels of hierarchical models: (1) unadjusted model; (2) case mix-adjusted models that included age, sex, race/ethnicity, diabetes mellitus, vascular access type, spKt/V, and  $rCL_{urea}$  at baseline as well as the nine preexisting comorbidities listed in Table 1; and (3) case mix- and malnutrition-inflammation cachexia syndrome (MICS)-adjusted models that included all above-mentioned covariates plus surrogates of nutritional and inflammatory status, including body mass index and 11 laboratory variables listed in Table 1. For models evaluating changes in nPCR, adjustment

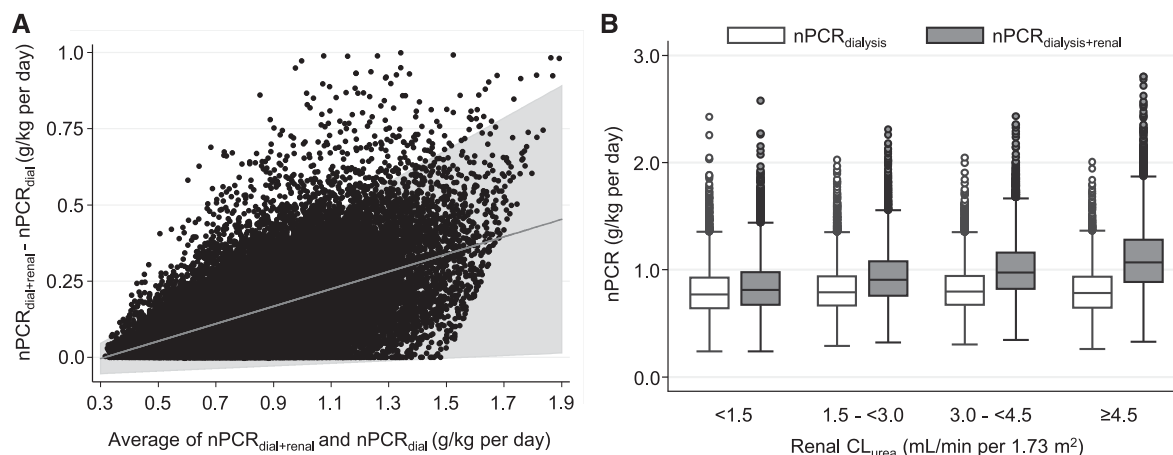
**Table 1. Baseline characteristics of 36,757 patients on incident hemodialysis according to renal CL<sub>urea</sub>-corrected nPCR level**

Variable	Total, n=36,757	renal CL <sub>urea</sub> -corrected nPCR at baseline		Std Diff.
		<1.2, n=29,685	≥1.2, n=7072	
Baseline nPCR, g/kg per day	0.94 (0.77–1.14)	0.87 (0.73–1.01)	1.35 (1.27–1.50)	2.95
Age, yr	62±15	62±15	61±14	0.08
Women, %	37	39	29	0.21
<b>Race/ethnicity, %</b>				
Non-Hispanic white	54	54	54	0.01
Black	28	30	19	0.27
Hispanic	11	10	16	0.20
Asian	3	3	7	0.19
Others	3	3	5	0.07
<b>ESRD reason, %</b>				
Diabetes	47	46	48	0.04
Hypertension	28	29	26	0.05
GN	10	10	11	0.03
Cystic kidney disease	2	2	2	0.04
Others	13	13	13	0.02
<b>Access type, %</b>				
Central venous catheter	74	75	71	0.09
AV fistula	18	17	22	0.12
AV graft	4	4	3	0.04
AV other	<0.1	<0.1	<0.1	0.00
Unknown	4	4	4	0.00
<b>Comorbidity, %</b>				
Hypertension	50	51	48	0.06
Atherosclerotic heart disease	14	14	14	0.01
Congestive heart failure	38	38	37	0.01
Cerebrovascular disease	2	2	1	0.04
Other cardiovascular disease	15	16	14	0.03
History of cancer	2	3	2	0.02
HIV	0.4	0.4	0.4	0.02
COPD	5	5	4	0.04
Dyslipidemia	26	26	27	0.02
spKt/V	1.55±0.36	1.53±0.35	1.66±0.39	0.37
Body mass index, kg/m <sup>2</sup>	27.4 (23.6–32.7)	27.5 (23.7–32.9)	26.9 (23.4–31.9)	0.08
Renal CL <sub>urea</sub> , ml/min per 1.73 m <sup>2</sup>	2.92 (1.54–4.76)	2.62 (1.36–4.30)	4.38 (2.74–6.42)	0.70
<b>Laboratories</b>				
WBC, 1000/μl	7.5 (6.1–9.0)	7.5 (6.1–9.0)	7.5 (6.2–9.0)	0.03
Lymphocyte, %	21±7	21±7	20±7	0.09
Hemoglobin, g/dl	11.2±1.1	11.2±1.1	11.4±1.1	0.21
Albumin, g/dl	3.57±0.46	3.54±0.46	3.69±0.41	0.34
Corrected calcium, mg/dl	9.1±0.5	9.1±0.5	9.0±0.6	0.14
Phosphorus, mg/dl	5.0±1.1	4.9±1.1	5.3±1.2	0.34
Intact PTH, pg/ml	314 (202–479)	310 (199–478)	328 (216–482)	0.07
ALP, IU/L	84 (67–110)	85 (68–111)	81 (64–105)	0.15
Creatinine, mg/dl	5.9±2.4	5.8±2.3	6.1±2.4	0.14
TIBC, mg/dl	230 (201–260)	227 (198–257)	241 (214–271)	0.35
Transferrin saturation, %	23±8	23±8	23±8	0.11
Ferritin, ng/ml	268 (157–451)	269 (157–453)	268 (156–445)	0.01
Bicarbonate, mEq/L	23.5±2.6	23.7±2.6	22.7±2.6	0.37

Continuous values are expressed as mean±SD if normally distributed or median (interquartile range) if skewed. Differences in patient characteristics between two groups were compared by Std Diff., of which 0.8, 0.5, and 0.2 were considered large, medium, and small differences, respectively, and ≥0.1 was defined as meaningful imbalance. nPCR<sub>dial+renal</sub>, normalized protein catabolic rate<sub>dialysis+renal</sub>; Std Diff., standardized difference; nPCR, normalized protein catabolic rate; AV, arteriovenous; COPD, chronic obstructive pulmonary disease; spKt/V, single-pool Kt/V; CL<sub>urea</sub>, urea clearance; WBC, white blood cell; PTH, parathyroid hormone; ALP, alkaline phosphatase; TIBC, total iron binding capacity.

for baseline nPCR was added to all models. Missing data in covariates (<1% for most laboratory variables and 4% for serum creatinine) were imputed by the mean or median of the

existing values as appropriate. All analyses were carried out using STATA MP, version 13.1 (StataCorp, College Station, TX).



**Figure 1. | Normalized protein catabolic rate (nPCR) was substantially underestimated among patients with residual kidney function when renal urea clearance ( $rCL_{urea}$ ) was not accounted for.** Comparison between baseline  $rCL_{urea}$ -corrected nPCR ( $nPCR_{dial}$ ) and baseline non- $rCL_{urea}$ -corrected nPCR ( $nPCR_{dial+renal}$ ) in (A) the Bland–Altman plot and (B) the box plot according to  $rCL_{urea}$  categories.

## Results

### Differences between Baseline nPCR Values with and without Accounting for $rCL_{urea}$

Median values (IQR) of  $nPCR_{dial}$  and  $nPCR_{dial+renal}$  at baseline were 0.78 (0.65–0.94) and 0.94 (0.77–1.14) g/kg per day, respectively. The median (IQR) difference between these two indices was 0.14 (0.07–0.23) g/kg per day. There was a trend toward larger differences between these two indices across higher averaged values of  $nPCR_{dial}$  and  $nPCR_{dial+renal}$  (Figure 1A). Patients with greater  $rCL_{urea}$  had higher  $nPCR_{dial+renal}$ ; among patients with  $rCL_{urea}$  <1.5, 1.5 to <3.0, 3.0 to <4.5, and  $\geq 4.5$  mL/min per  $1.73\text{ m}^2$ ,  $nPCR_{dial+renal}$  showed consistently higher values with median (IQR) values of 0.81 (0.67–0.98), 0.91 (0.76–1.08), 0.98 (0.82–1.16), and 1.07 (0.89–1.28), respectively, while median (IQR) values of  $nPCR_{dial}$  were 0.77 (0.64–0.93), 0.79 (0.66–0.94), 0.80 (0.67–0.94), and 0.78 (0.65–0.94) g/kg per day, respectively. Differences between  $nPCR_{dial}$  and  $nPCR_{dial+renal}$  were significantly larger across higher  $rCL_{urea}$  categories: 0.04 (95% confidence interval [95% CI], 0.01 to 0.06), 0.11 (95% CI, 0.09 to 0.14), 0.18 (95% CI, 0.14 to 0.22),

and 0.28 (95% CI, 0.21 to 0.36) g/kg per day, respectively ( $P_{interaction} < 0.001$ ) (Figure 1B).

### Baseline Demographic, Clinical, and Laboratory Characteristics according to Baseline $rCL_{urea}$ -Corrected nPCR

Among 36,757 patients, the mean  $\pm$  SD age was  $62 \pm 15$  years old, 37% were women, 54% were non-Hispanic white, 28% were black, and 47% had diabetes as the cause of ESRD (Table 1). Patients were dichotomized on the basis of baseline  $nPCR_{dial+renal}$  <1.2 g/kg per day ( $n=29,685$ ; 81%) versus  $\geq 1.2$  g/kg per day ( $n=7,072$ ; 19%). The latter nPCR range is the recommended target range set forth by the KDOQI clinical practice guidelines (8). Compared with patients with  $nPCR_{dial+renal}$  <1.2 g/kg per day at baseline, those who had greater  $nPCR_{dial+renal}$  ( $\geq 1.2$  g/kg per day) were more likely to be men and Hispanic or Asian and less likely to be black; were more likely to use arteriovenous fistula; had higher spKt/V,  $rCL_{urea}$ , hemoglobin, albumin, phosphorus, creatinine, and total iron binding capacity; and had lower serum calcium, alkaline phosphatase, and bicarbonate.

**Table 2. Categories of baseline renal urea clearance-corrected normalized protein catabolic rate ( $nPCR_{dial+renal}$ ) in 36,757 incident patients**

Baseline $nPCR_{dial+renal}$ , g/kg per day	Group Size, n (% of Total)	Mean $\pm$ SD Baseline Serum Albumin, g/dl	All-Cause Death per 100 patient-yr (n)
<0.6	2571 (7)	$3.24 \pm 0.54$	20.8 (774)
0.6 to <0.7	3384 (9)	$3.42 \pm 0.48$	17.9 (959)
0.7 to <0.8	4757 (13)	$3.50 \pm 0.45$	15.4 (1198)
0.8 to <0.9	5558 (15)	$3.56 \pm 0.44$	13.8 (1336)
0.9 to <1.0	5337 (15)	$3.61 \pm 0.42$	12.7 (1191)
1.0 to <1.1	4594 (13)	$3.64 \pm 0.42$	12.6 (1011)
1.1 to <1.2	3484 (9)	$3.65 \pm 0.42$	11.4 (717)
1.2 to <1.3	2521 (7)	$3.68 \pm 0.41$	10.4 (479)
1.3 to <1.4	1660 (5)	$3.69 \pm 0.41$	10.2 (305)
$\geq 1.4$	2891 (8)	$3.69 \pm 0.42$	10.1 (511)
Total	36,757 (100)	$3.57 \pm 0.46$	13.5 (8481)



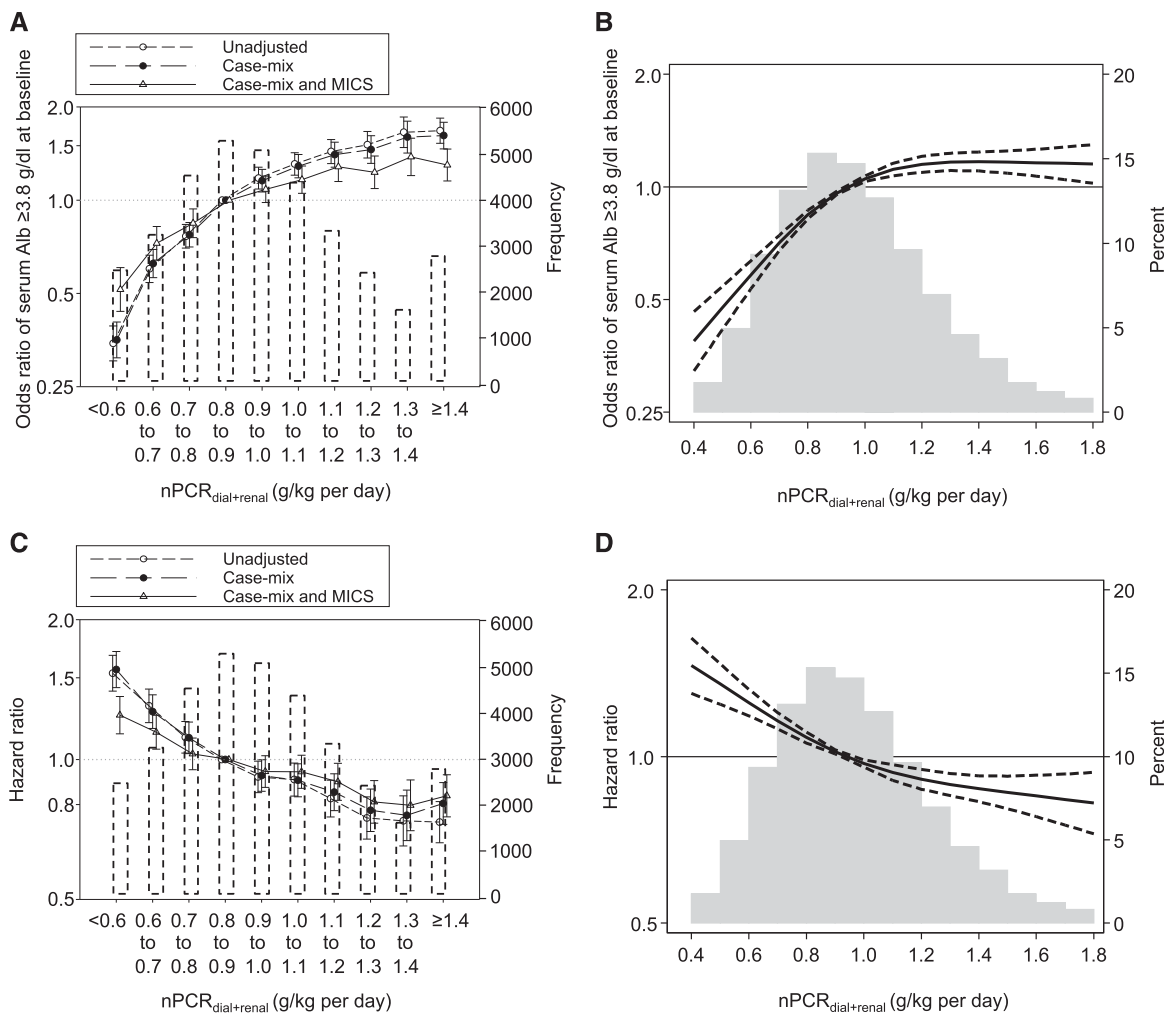
### Association of Baseline $\text{rCL}_{\text{urea}}$ -Corrected nPCR with Serum Albumin Levels and All-Cause Mortality

A total of 8481 deaths were observed during the follow-up period (up to 5 years; median [IQR] = 1.4 [0.7–2.5] years), with a mortality rate of 13.5/100 patient-yr. There was an unadjusted trend toward higher baseline serum albumin across higher baseline  $\text{nPCR}_{\text{dial+renal}}$  categories (Table 2), which were robust against adjustments ( $P_{\text{trend}} < 0.001$  for all models) (Figure 2A, Supplemental Table 2). Additionally, there was a consistent trend toward lower mortality risk across higher  $\text{nPCR}_{\text{dial+renal}}$  irrespective of adjustment model, albeit with an attenuation in the fully adjusted model ( $P_{\text{trend}} < 0.001$  for all models) (Table 2, Figure 2C, Supplemental Table 3). Compared with the reference group (0.8–0.9 g/kg per day), baseline  $\text{nPCR}_{\text{dial+renal}} < 0.7$  g/kg per day was significantly associated with higher mortality; fully adjusted hazard ratio (HRs) were 1.25 (95% CI, 1.14 to 1.37) and 1.14 (95% CI, 1.05 to 1.24) for  $\text{nPCR}_{\text{dial+renal}} < 0.6$

and 0.6 to  $< 0.7$  g/kg per day, respectively. Patients with  $\text{nPCR}_{\text{dial+renal}} \geq 1.1$  g/kg per day had a lower mortality risk compared with the referent: fully adjusted HRs, 0.89 (95% CI, 0.81 to 0.98), 0.81 (95% CI, 0.73 to 0.90), 0.79 (95% CI, 0.69 to 0.89), and 0.83 (95% CI, 0.75 to 0.92) for  $\text{nPCR}_{\text{dial+renal}} = 1.1$ –1.2, 1.2–1.3, 1.3–1.4, and  $\geq 1.4$  g/kg per day, respectively. Consistent results were observed in the models using restricted cubic spline functions (Figure 2B and D).

### Association of Change in $\text{rCL}_{\text{urea}}$ -Corrected nPCR with Serum Albumin Level and All-Cause Mortality

Among 13,895 patients, patients with a greater rise in  $\text{nPCR}_{\text{dial+renal}}$  had lower baseline  $\text{nPCR}_{\text{dial+renal}}$  and serum albumin (Table 3). There was a consistent trend toward higher likelihood of having serum albumin  $\geq 3.8$  g/dl at the third patient-quarter across greater rise in  $\text{nPCR}_{\text{dial+renal}}$  categories, irrespective of adjustment model and without attenuation ( $P_{\text{trend}} < 0.001$  for all models) (Figure 3A,



**Figure 2. | Higher baseline renal urea clearance-corrected normalized protein catabolic rate ( $\text{nPCR}_{\text{dial+renal}}$ ) levels were associated with higher likelihood of having baseline serum albumin (Alb)  $\geq 3.8$  g/dl and lower mortality among 36,757 incident hemodialysis patients.** Likelihood of having baseline serum Alb  $\geq 3.8$  g/dl using (A) baseline  $\text{nPCR}_{\text{dial+renal}}$  categories with three-level hierarchical adjustment models and (B) restricted cubic splines in the fully adjusted model. Association between baseline  $\text{nPCR}_{\text{dial+renal}}$  and mortality using (C) baseline  $\text{nPCR}_{\text{dial+renal}}$  categories with three-level hierarchical adjustment models, and (D) restricted cubic splines in the fully adjusted model. The histograms in (A) and (C) show the number of patients in each category. (B) and (D) were truncated at the first and 99th percentiles of data. MICS, malnutrition-inflammation cachexia syndrome.

Supplemental Table 4). Consistent results were also observed in models using restricted cubic spline functions (Figure 3B). Similarly, greater rise in  $nPCR_{dial+renal}$  was also associated with higher likelihood of an increase in serum albumin  $\geq 0.2$  g/dl per 6 months (Supplemental Figure 2).

Among 13,895 patients with available data on change in  $nPCR_{dial+renal}$ , 2877 patients died during the follow-up period (up to 4.5 years; median [IQR] = 1.5 [0.8–2.4] years). Greater rise in  $nPCR_{dial+renal}$  categories had lower overall crude rates of all-cause death, despite lower baseline  $nPCR_{dial+renal}$  and serum albumin ( $P_{trend} < 0.001$ ) (Table 3). There was an inverse linear relationship between change in  $nPCR_{dial+renal}$  and mortality risk ( $P_{trend} < 0.001$  for all models) (Figure 3C, Supplemental Table 5). Compared with the reference group (a rise of 0.1–0.2 g/kg per day between the first and third patient-quarters), a decline in  $nPCR_{dial+renal} \geq 0.1$  g/kg per day was significantly associated with higher mortality risk: HR, 1.32 (95% CI, 1.14 to 1.54) and HR, 1.22 (95% CI, 1.04 to 1.42) for decrease in  $nPCR_{dial+renal} > 0.2$  and  $> 0.1$ –0.2 g/kg per day, respectively. However, a rise in  $nPCR_{dial+renal} \geq 0.4$  g/kg per day showed a lower mortality risk in fully adjusted models: HR, 0.82 (95% CI, 0.69 to 0.97) and HR, 0.76 (95% CI, 0.64 to 0.90) for rise in  $nPCR_{dial+renal} = 0.4$ –0.5 and  $> 0.5$  g/kg per day, respectively. Consistent results were also observed in models using restricted cubic splines (Figure 3D).

#### Mortality Risk Associated with Discordance between $nPCR$ Values with versus without Accounting for $rCL_{urea}$

To examine the mortality risk associated with discordance between  $nPCR$  values with versus without accounting for  $rCL_{urea}$ , we conducted a Cox regression analysis with case-mix adjustment after categorizing patients according to  $nPCR_{dial+renal}$  and  $nPCR_{dial}$  values (*i.e.*,  $< 0.8$ , 0.8 to  $< 1.0$ , 1.0 to  $< 1.2$ , and  $\geq 1.2$  g/kg per day). For example, among 10,827 patients who were categorized as having  $nPCR_{dial}$  levels of 0.8 to  $< 1.0$  g/kg per day, there were 3659 (34%) who were concordantly categorized as having  $nPCR_{dial+renal}$  levels of 0.8 to  $< 1.0$  g/kg per day (Figure 4A). There was an incrementally lower risk of all-cause death across increasing  $nPCR_{dial+renal}$  categories within each category of  $nPCR_{dial}$  ( $P_{trend} < 0.001$ ) (Figure 4B). However, this relationship

did not persist on examination from the opposite axis. Among patients who were categorized as having  $nPCR_{dial+renal}$  levels of 0.8 to  $< 1.0$  g/kg per day, the adjusted mortality risk was paradoxically higher in greater  $nPCR_{dial}$  values (*i.e.*, HR, 1.13 [95% CI, 1.00 to 1.27] in  $< 0.8$  g/kg per day versus HR, 1.21 [95% CI, 1.07 to 1.37] in 0.8 to  $< 1.0$  g/kg per day;  $P = 0.04$ ). Furthermore, there were no significant trends observed across categories of  $nPCR_{dial}$  within the other  $nPCR_{dial+renal}$  categories ( $P_{trend} = 0.73$  in 1.0 to  $< 1.2$  g/kg per day and  $P_{trend} = 0.46$  in  $\geq 1.2$  g/kg per day).

#### Discussion

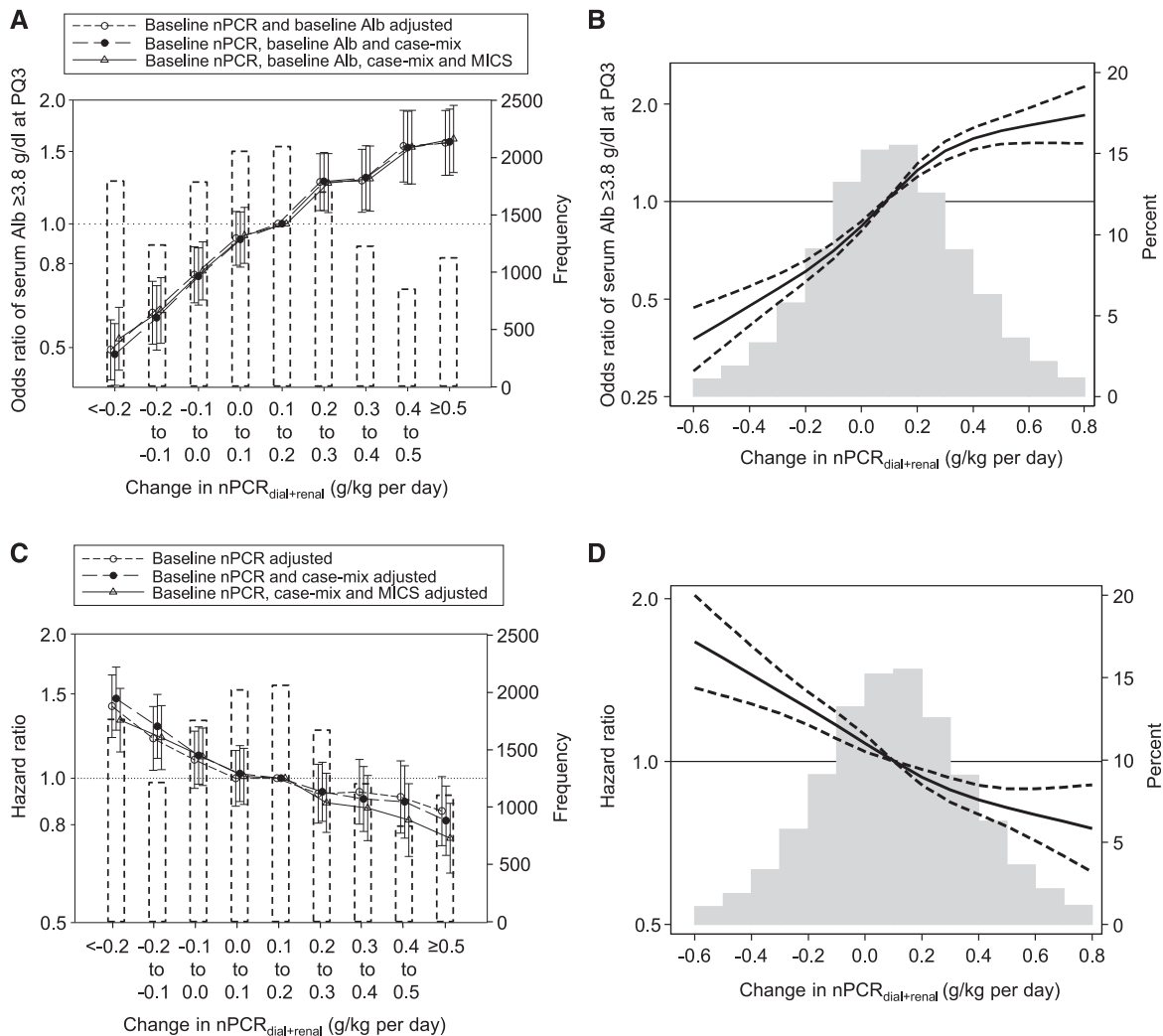
In this longitudinal and national cohort of over 36,000 incident hemodialysis patients with documented data on residual kidney function, we found that  $nPCR$  without accounting for  $rCL_{urea}$  tended to underestimate  $nPCR$  values, especially among patients with greater  $rCL_{urea}$ . We also showed that baseline  $nPCR_{dial+renal}$  (*i.e.*,  $rCL_{urea}$ -corrected  $nPCR$ ) was inversely associated with mortality. Additionally, change in  $nPCR_{dial+renal}$  during the first 6 months of hemodialysis was a significant correlate of attaining high serum albumin and mortality risk independent of baseline  $nPCR_{dial+renal}$  and other MICS markers. To our knowledge, this is the first study to examine the association of  $nPCR$  with serum albumin levels and mortality accounting for the contribution of  $rCL_{urea}$ .

In current clinical practice,  $nPCR$  is calculated without accounting for  $rCL_{urea}$ , resulting in the underestimation of total urea excretion from the body among patients with residual kidney function. One previous study showed that there was no association of  $nPCR$  at either baseline or 6 months follow-up with mortality outcomes (14). However, it was acknowledged in this study that there may be bias toward the null due to lack of uniformity of the postdialysis blood flow for BUN measurement, which may have affected the precision of  $nPCR$  values (14). Given the large error in calculation of  $nPCR$  and the strong association with patient health-related quality of life and clinical outcomes, we believe that  $rCL_{urea}$  should be periodically monitored and accounted for when evaluating protein intake using  $nPCR$  among patients with residual kidney function.

Our study showed a clear inverse linear trend toward lower mortality across higher  $nPCR_{dial+renal}$ , whereas

**Table 3. Categories of change in renal urea clearance-corrected normalized protein catabolic rate ( $nPCR_{dial+renal}$ ) during the first 6 months in 13,895 incident hemodialysis patients**

Change in $nPCR_{dial+renal}$ , g/kg per day	Group Size (% of Total)	Mean $\pm$ SD Baseline $nPCR_{dial+renal}$ , g/kg per day	Mean $\pm$ SD Baseline Serum Albumin, g/dl	All-Cause Death, per 100 patient-yr ( <i>n</i> )
$< -0.2$	1802 (13)	$1.32 \pm 0.31$	$3.67 \pm 0.42$	12.8 (369)
$-0.2$ to $< -0.1$	1235 (9)	$1.10 \pm 0.25$	$3.65 \pm 0.44$	13.1 (277)
$-0.1$ to $< 0.0$	1793 (13)	$1.02 \pm 0.24$	$3.65 \pm 0.43$	12.6 (391)
0.0 to $< 0.1$	2061 (15)	$0.97 \pm 0.24$	$3.62 \pm 0.44$	12.0 (422)
0.1 to $< 0.2$	2102 (15)	$0.93 \pm 0.24$	$3.63 \pm 0.43$	12.3 (434)
0.2 to $< 0.3$	1704 (12)	$0.90 \pm 0.22$	$3.58 \pm 0.44$	11.9 (344)
0.3 to $< 0.4$	1227 (9)	$0.89 \pm 0.23$	$3.58 \pm 0.45$	12.1 (251)
0.4 to $< 0.5$	851 (6)	$0.87 \pm 0.24$	$3.53 \pm 0.44$	12.1 (181)
$\geq 0.5$	1120 (8)	$0.85 \pm 0.24$	$3.51 \pm 0.45$	11.4 (208)
Total	13,895 (100)	$1.00 \pm 0.29$	$3.61 \pm 0.44$	12.3 (2877)



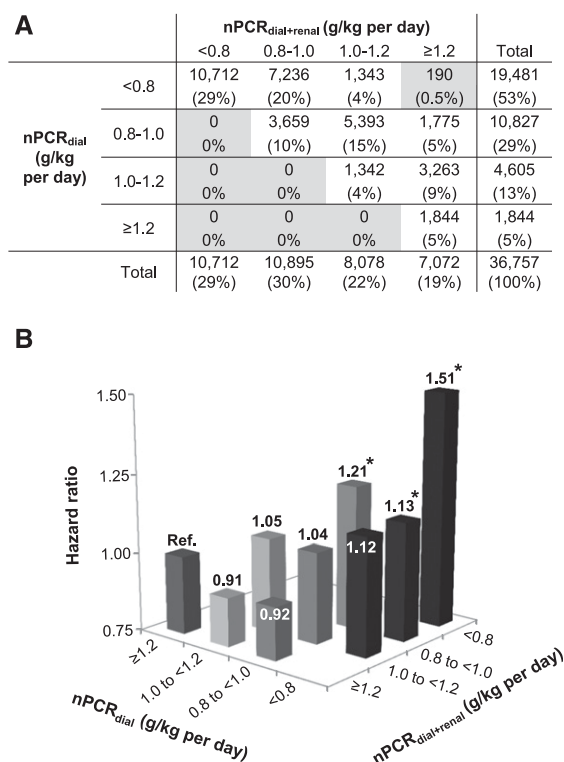
**Figure 3. | Greater increase in renal urea clearance-corrected normalized protein catabolic rate (nPCR<sub>dial+renal</sub>) between the first and the third patient-quarter was associated with higher likelihood of attaining serum albumin (Alb)  $\geq 3.8$  g/dl at the third patient-quarter and lower mortality among 13,895 incident hemodialysis patients.** Likelihood of attaining serum Alb  $\geq 3.8$  g/dl at 6 months after dialysis initiation using (A) change in nPCR<sub>dial+renal</sub> categories with three-level adjustment models and (B) restricted cubic splines in the fully-adjusted model. Association between change in nPCR<sub>dial+renal</sub> using (C) change in nPCR<sub>dial+renal</sub> categories with three-level adjustment models and (D) restricted cubic splines in the fully adjusted model. The histograms in (A) and (C) show the number of patients in each category. (B) and (D) were truncated at the first and 99th percentiles of data. MICS, malnutrition-inflammation cachexia syndrome; PQ3, third patient-quarter.

previous studies have shown a reverse J-shaped association, where patients with nPCR<sub>dial</sub>  $\geq 1.4$  g/kg per day had a higher mortality risk (16,17). The association between nPCR<sub>dial+renal</sub> and mortality in our study was robust, even after rigorous adjustment for case mix variables and MICS markers. The difference in results between our study and the previous studies is likely attributed to the difference between nPCR<sub>dial</sub> and nPCR<sub>dial+renal</sub>; the differences between these two variables are especially greater among patients with higher nPCR levels (Figure 1). In our study, there also seemed to be an incrementally higher mortality risk associated with lower nPCR<sub>dial+renal</sub> levels within the same nPCR<sub>dial</sub> category, suggesting that a better risk stratification of all-cause mortality attributed to nPCR accounting for rCL<sub>urea</sub>. The paradoxically lower mortality risk associated with lower nPCR<sub>dial</sub> among patients who were categorized as having low nPCR<sub>dial+renal</sub> (*i.e.*, 0.8–

<1.0 g/kg per day) may be due to residual kidney function, a strong predictor of better survival among patients on hemodialysis (19,20).

Higher rise in nPCR<sub>dial+renal</sub> was a correlate of attaining higher serum albumin at the third patient-quarter, despite lower baseline nPCR<sub>dial+renal</sub> and serum albumin. Inflammation decreases serum albumin levels by reducing the rate of synthesis *via* downregulation of albumin gene transcription (26–29). Malnutrition and inflammation are closely related to each other and orchestrate the development of PEW (3,5), and recent randomized clinical trials showed that protein supplementation reduced inflammation and increased serum albumin levels (30,31). Moreover, higher rise in nPCR<sub>dial+renal</sub> predicted lower mortality. These associations between baseline or change in nPCR<sub>dial+renal</sub> and mortality seemed to be attenuated in the fully adjusted model, but it is likely due to overadjustment for MICS markers, which also included





**Figure 4. | Normalized protein catabolic rate (nPCR) was underestimated according to renal urea clearance (rCL<sub>urea</sub>) levels among 36,757 incident hemodialysis patients, leading to an overestimation of all-cause mortality risk associated with low nPCR. (A) Concordance and discordance of rCL<sub>urea</sub>-corrected nPCR (nPCR<sub>dial+renal</sub>) and non-rCL<sub>urea</sub>-corrected nPCR (nPCR<sub>dial</sub>) and (B) mortality risk associated with categories defined by the combination of nPCR<sub>dial</sub> and nPCR<sub>dial+renal</sub> among 36,757 incident hemodialysis patients in a case mix-adjusted model. Gray cells in A indicate groups in which hazard ratios were not reported due to the limited number of patients. \* $P < 0.05$ .**

serum albumin and other potential intermediate factors in the causal pathway between dietary protein intake and survival. Rise in nPCR over the first 6 months of dialysis may be one of the representations of increased appetite and intake in relation to the resolution of uremic symptoms (32). Nevertheless, baseline or change in nPCR<sub>dial+renal</sub> was independently associated with all-cause death even after adjustment for MICS-related variables. Therefore, nPCR may be a useful predictor of mortality in patients on hemodialysis among others (3,33) as included in composite nutritional scores (34,35).

Several limitations of our study should be noted. First, there are day-to-day fluctuations in nPCR caused by changes in daily protein intake (36). However, the use of nPCR data that were averaged over a treatment quarter might mitigate the effect of these fluctuations on our examined associations. Second, the use of nPCR as a reflection of daily protein intake assumes that protein metabolism is in equilibrium at the time of measurement (37). This is not always the case with patients on hemodialysis, because they are susceptible to various comorbidities, which may induce protein catabolism. Additionally, information about rCL<sub>urea</sub> was not available for all patients. Therefore, our results may not be representative of the entire cohort and may be subject to selection biases. As shown in Supplemental Table 1, patients with available rCL<sub>urea</sub>

were more likely to be non-Hispanic white and had higher spKt/V, albumin, and body mass index. However, adding rCL<sub>urea</sub> data to the calculation of nPCR may have provided a more accurate approach in evaluating nPCR. Although we adjusted for a number of inflammatory markers, such as serum ferritin, total iron binding capacity, blood white blood cells, and lymphocyte percentage (38–40), other inflammatory markers, such as C-reactive protein, were not available.

In conclusion, our study shows that both higher baseline values and greater increase in dietary protein intake, represented by rCL<sub>urea</sub>-corrected nPCR, are independently associated with attaining higher serum albumin levels and lower all-cause mortality among incident hemodialysis patients. Compared with conventional nPCR, rCL<sub>urea</sub>-corrected nPCR may be a better marker of mortality among patients on hemodialysis with substantial residual kidney function. Future studies should investigate effective nutrition treatments in patients on hemodialysis and their effects on clinical outcomes.

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